REVIEW ARTICLE

Advances in the Theory and Practice of Exchange Transfusions

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■ *In the management and prevention of hemolytic disease of the newborn, exchange transfusions seem destined to remain the mainstay of therapy for some time to come.*

Our current knowledge of bilirubin metabolism has altered the indications for the procedure and introduced such useful new adjuncts to therapy as albumin infusions. The decision to do an exchange transfusion cannot be made by any one rule, but must be individualized for each patient and take into account all the factors known to influence the risks of bilirubin toxicity and the exchange procedure. A thorough evaluation of the infant's condition, particularly his cardiorespiratory and metabolic status (including blood pH, gas and albumin determinations), will provide valuable information as a guide to therapy. The limited capacity of some newborn infants to make adequate physiological adaptations to a variety of stresses imposed by the procedure influences the preparation of donor blood, the rate and volume of exchange and the time at which it should be done.

A clear understanding of the mechanics of the exchange and the distribution of indirect bilirubin within the body will permit more accurate prediction of what can be accomplished in bilirubin removal and correction of hematocrit with exchanges of different volumes. When weighing the risk of kernicterus against that of exchange transfusion, the experience of the operator and the availability of suitable facilities cannot be ignored.

EXCHANGE TRANSFUSION, the mainstay for the treatment of hemolytic disease of the newborn (HDN) for the past two decades, can achieve three things: (1) With sedimented red cells, it can raise the hematocrit without increasing the blood volume of a severely affected erythroblastotic newborn infant in the first minutes of life; (2) It can remove antibody-coated cells from the involved newborn infant's circulation before they hemolyze and produce bilirubin; and (3) It can remove bilirubin in the circulating plasma and some from extravascular areas, so that its concentration can be kept below levels which are generally considered to be toxic to tissues—particularly central nervous system tissues.* New diagnostic and therapeutic

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*Direct van den Bergh reacting bilirubin or glucuronide conjugated bilirubin is considered to be non-toxic. Indirect reacting or unconjugated bilirubin is the dangerous fraction, and throughout this paper *bilirubin* refers only to this fraction. The importance of a uniform laboratory standard for indirect bilirubin has been emphasized recently.[2]

developments include amniocentesis, intraperitoneal transfusion and prevention of maternal sensitization.

Amniocentesis. Spectrophotometric analysis of amniotic fluid obtained by amniocentesis permits accurate prediction of the presence of isoimmune hemolytic disease in the fetus, assessment of severity of disease, and prediction as to which infants should be delivered before 40 weeks of gestation to prevent intrauterine death.[9]

Intrauterine intraperitoneal transfusions are used for severely affected fetuses to keep them alive and healthy long enough so that the pregnancy may be carried to a point where the newborn infant will not be too small or anemic and hydropic to be saved.[10,11] A few fetuses that receive intrauterine transfusions absorb so much of the donor blood into the circulation that erythropoiesis is suppressed; there are no Rh-positive cells in their circulation to be hemolyzed to produce bilirubin, so that they do not need exchange transfusions. Most of these infants, however, need multiple exchange transfusions after birth.

Intrauterine transfusions of moderately affected fetuses might eliminate the need for many exchange transfusions after birth; however, this would replace a relatively safe and highly effective form of therapy with one which still carries a high fetal mortality and is rightly reserved for only the desperately ill fetus.

Maternal sensitization. Injection of anti-Rh antibodies into Rh-negative mothers with Rh-positive husbands is being studied as a means of preventing maternal sensitization and production of massive amounts of antibodies.[6] This offers hope for preventing HDN and eliminating the need for most exchange transfusions. But, even if effective, a massive program would have to be carried out before there was a population free of sensitized Rh-negative mothers, and it would not eliminate isoimmunization due to other blood groups.

Indications for Exchange Transfusion

The first consideration in exchange transfusion is the indication for the procedure itself. If an affected baby at birth is significantly anemic, is hyperbilirubinemic and has increased concentrations of reticulocytes and nucleated red cells in the peripheral blood, kernicterus is likely to develop unless an exchange transfusion is performed. These infants must have an exchange transfusion in the first two to 24 hours of life, and may require a *small* exchange with sedimented erythrocytes in the first few hours of life if the anemia is severe enough to produce signs and symptoms of cardiorespiratory embarrassment.

Most infants, however, are not so severely affected. The objective is to keep the concentration of bilirubin at so low a level that the chance for kernicterus to develop is no greater than the risk of the exchange procedure itself. The higher the peak level of bilirubin, the greater the chances for kernicterus.[1] The key question, then, is: What is the level of bilirubin at which the chances that kernicterus will develop, equal or surpass the possibility of death due to the procedure itself (which should be about 1 per cent or less in term infants without hydrops or respiratory distress)? This is still a controversial question. The toxic effects of indirect bilirubin upon the central nervous system are a function of a variety of physiological variables in addition to the plasma concentration of bilirubin.

There is as yet insufficient clinical data to evaluate the relative importance of each variable. McKay[12] has summarized the problem as follows:

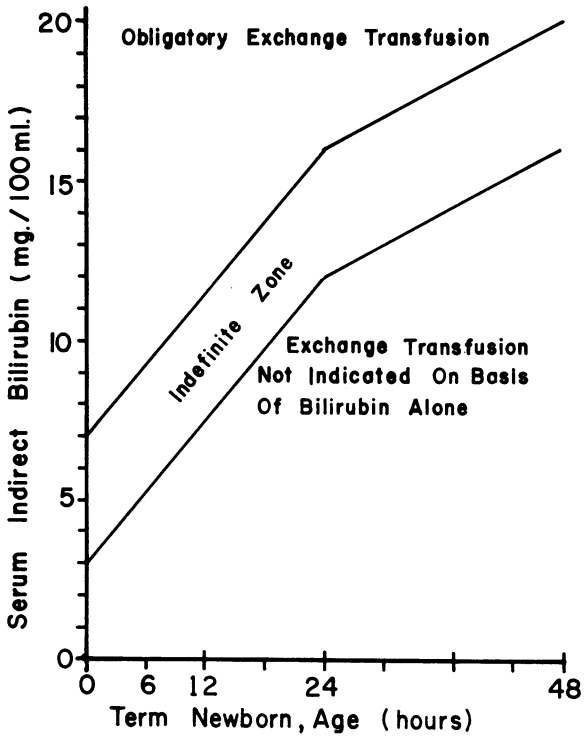

Chart 1A.—Chart for using serum indirect bilirubin concentrations as the sole indication for exchange transfusion in mature infants. An infant with hemolytic disease of the newborn and indirect bilirubin measurements above the upper line is a candidate for exchange transfusion on the basis of the bilirubin alone.

"The only absolute indication for exchange transfusion is the appearance of clinical signs of *early* kernicterus, whatever the level of serum bilirubin." He is quick, however, to point out that clinicians must use the available but incomplete data to evaluate the risk of kernicterus in each individual patient in terms of all the variables.

Bilirubin. The critical concentration of bilirubin is not in the plasma but within the cell, where its toxic properties interfere with oxidative metabolism—probably by a toxic effect upon the mitochondria.[13] Though plasma and intracellular concentrations of bilirubin are related, one is not a direct measurement of the other. Much of the extracellular bilirubin is bound to albumin and does not enter a cell easily. By raising the concentration of albumin to a level at which its bilirubin-binding capacity exceeds the amount of bilirubin present, bilirubin will be prevented from going into cells and its toxic effect will be blocked. At such concentrations of albumin, intracellular bilirubin is drawn out slowly into the extracellular fluid.[5,20] Even the intracellular concentration may have a variable toxicity, depending upon the condition in the individual cell—a hypoxic or acidotic cell may be more sensitive.

Originally, clinical evaluation in hemolytic disease due to Rh or ABO incompatibility correlated the peak level of serum bilirubin, the severity of hemolysis and maturity with the chances for kernicterus.[1] The critical level of bilirubin concentration was considered to be 20 mg per 100 ml in full-term newborns and 18 mg per 100 ml in prematures; below these levels, the chances for kernicterus to develop were less than 5 per cent, perhaps as low as 2 to 3 per cent. Allen and Diamond[1] developed a useful chart for plotting serial determinations of bilirubin within the first 12 or 24 hours of life which indicated whether a baby would ultimately reach a concentration over 20 mg per 100 ml and require an exchange transfusion (Charts 1A and 1B).

Normal adult plasma has enough albumin to bind approximately 80 mg of bilirubin per 100 ml,[14] but the binding of bilirubin by albumin varies directly with pH and is diminished by other com-

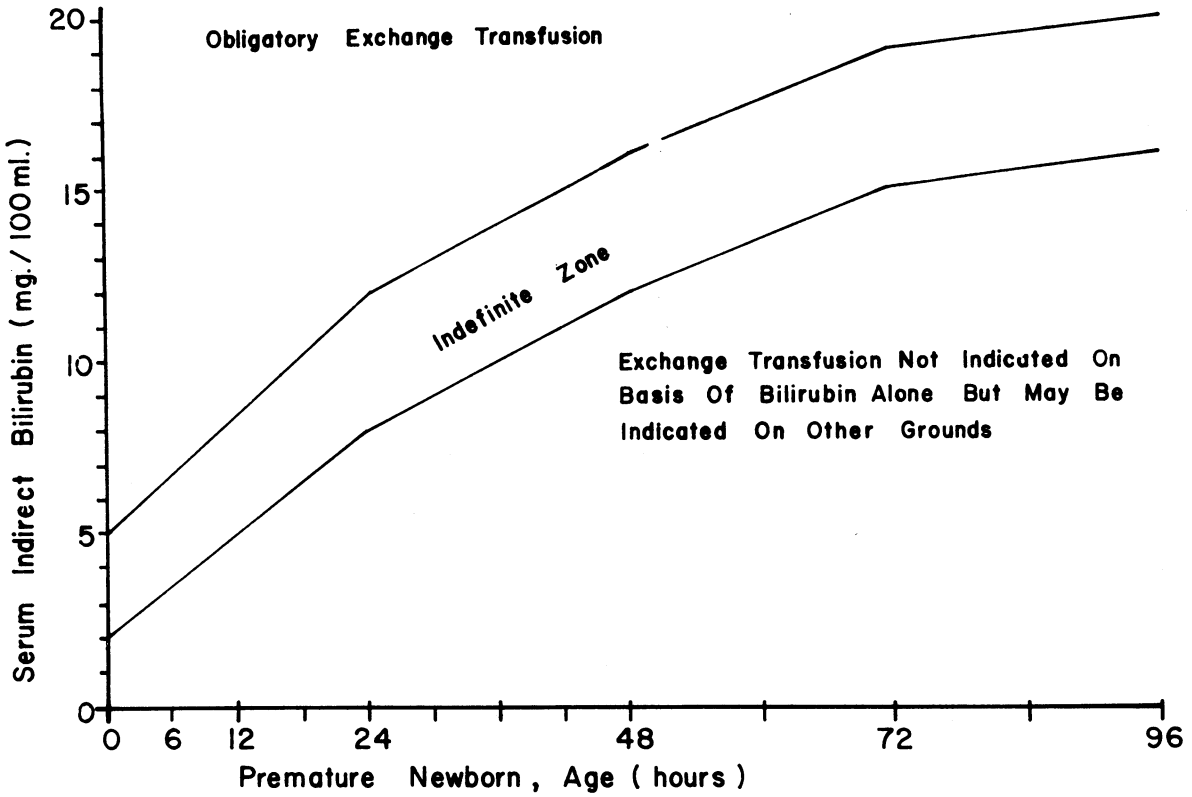

Chart 1B.—Chart for premature infants with hemolytic disease of the newborn. This chart and Chart 1A are meant to be tentative guides only. The indications for exchange transfusion which they define should be modified by the clinical findings and other laboratory studies on the individual patient. (Charts after Allen and Diamond, with the kind permission of Dr. F. H. Allen.)

pounds which bind competitively with albumin (sulfonamides, free fatty acids,* salicylates and certain other antimicrobial agents). Newborn infants have a low concentration of albumin. They are often acidotic and the pH of the extracellular fluid adjacent to a cell may be considerably less than in arterial blood, particularly in those cells at a distance from the nearest capillary. If peripheral circulation is poor, local metabolic acidosis will further lower the bilirubin-binding capacity of the albumin. Thus, acid base balance, regional microcirculation, presence of competitive binding substances and lower levels of albumin may make a given concentration of bilirubin much more toxic in one infant than in another.

Porter and Waters, attempting to improve criteria for doing exchange transfusions, measured the capacity of a given specimen of serum to bind more bilirubin.[17,21] So long as there is some residual binding capacity, the infant is presumed to be protected from the toxic effects of bilirubin. This measurement is more nearly definitive than that of serum bilirubin and albumin, but it has a serious drawback. What is actually measured is the capacity of plasma to bind a dye, not more bilirubin. The test is done at a pH of 7.4 and the binding of the dye is uninfluenced by changes in pH. This test might indicate a given bilirubin level was safe because at pH 7.4 an infant's plasma had the capacity to bind more bilirubin than was present. However, at the pH of the infant's blood, the binding capacity may have been exceeded and the bilirubin actually at a dangerous level. The laboratory value alone, therefore, cannot be taken as an indication for exchange transfusion, and the general condition of the infant must still be taken into account.

Cause of hyperbilirubinemia. The original data on the risk of kernicterus are for hyperbilirubinemia due to Rh and ABO-isoimmune hemolytic disease. At a given level of severity, disease due to ABO incompatibility is probably just as dangerous as Rh hemolytic disease.[1] Higher levels of bilirubin may be safe in ABO disease, but data are too scant to accept this dangerous assumption as an operating principle. Hemolytic diseases due to less common fetal-maternal incompatibilities, such as maternal anti-Kell, are not common enough to be evaluated separately at this time and should be considered as dangerous as Rh or ABO hemolytic disease.

*These are elevated when an infant has no source of carbohydrate.

Kernicterus due to non-hemolytic hyperbilirubinemia is well documented and can occur in prematures at low concentrations of bilirubin.[3,12] However, under equivalent conditions, a given concentration of bilirubin as the result of hemolytic disease seems to be more toxic than the same concentration due to other causes.[22] There are a number of possible explanations for this.

In isoimmune hemolytic disease of the newborn (HDN) the infant's erythrocytes are coated with maternal globulin which interferes with oxygen transport across the cell membrane. Furthermore, the breakdown products of hemoglobin released by hemolysis are present in higher concentrations. Carboxyhemoglobin may have a toxic effect upon the brain tissue, and heme products that are bound to albumin as methemalbumin may interfere with bilirubin binding.

Age. It has been suggested that with age the newborn's blood brain barrier may change so that bilirubin is no longer toxic and that, therefore, exchange transfusions are not needed after about five days of age. On the other hand, there is some evidence from animal experimentation that, under equivalent conditions, bilirubin enters brain tissue just as easily in adults as in newborns.[5] Clinically, kernicterus has been observed to develop after the first one or two weeks of life. The rarity of such cases is explained by the facts that (1) Such high levels of indirect bilirubin are seldom seen after the first week of life, and (2) By this age, those factors which enhance bilirubin toxicity are much less common. For the time being, one cannot consider bilirubin to be non-toxic at any level after the first week of life.

If all the critical factors and the relative importance of each variable were known, one could predict which 5 per cent of all full-term infants would develop kernicterus when the serum bilirubin exceeded 20 mg per 100 ml, which infants would be safe at a much higher level, and which were in danger at levels below it. Only some of these factors are known at present, but they are being used to alter the criteria for exchange transfusion.

Present criteria vary considerably from one medical center to another. The following is an attempt to summarize them.

In HDN due to Rh, ABO or any other incompatibility, the old standards (with modifications) still apply: In infants under two days of age, bilirubin levels are kept below 20 mg per 100 ml in full-term newborns and 18 mg per 100 ml in prema-

tures; from two to five days of age (10 days for small prematures) the same standards apply, except that the critical level of bilirubin should be found on two successive determinations four hours apart. (Other observers use 22 mg per 100 ml as the critical level in healthy full-term newborn infants.) The concentration at birth and the early rise of bilirubin (Charts 1A and 1B), the presence of such other findings as anemia (hemoglobin less than 11 gm per 100 ml) or hydrops, and previous maternal history* are guides for early exchange transfusion. The critical concentration for exchange transfusion is lowered by at least 2 to 4 mg per 100 ml in the presence of any of the factors known to increase the chance of bilirubin toxicity. However, the most common aggravating factors (the respiratory distress syndrome with its consequent hypoxia, acidosis and poor peripheral circulation) also make transfusion a more hazardous procedure.

In non-hemolytic jaundice, the critical level is about 5 mg per 100 ml higher than in similar infants with HDN—that is, 20 or 23 mg per 100 ml in healthy prematures and up to 25 mg per 100 ml in healthy full-term babies. Again the critical level is lowered by the presence of acidosis. Early signs of kernicterus are an indication for exchange transfusion regardless of the concentration and cause hyperbilirubinemia. (Lethargy, poor sucking, hypotonia and a poor Moro response generally precede the more classic and specific signs of fever, opisthotonos, high-pitched cry and a "sunset" appearance of the eyes.)

Donor Blood

Once exchange transfusion is decided upon, the appropriate donor blood should be available immediately so that the exchange can be done and, if necessary, repeated at the optimum time. The physician should not, at that late date, begin to arrange for an appropriate unit or units of donor blood. Bilirubin levels can rise to dangerous levels during a belated search for appropriate donor blood. If a woman has a history of babies affected with Rh hemolytic disease, or if evaluation of the amniotic fluid suggests moderate or severe hemolysis, packed or sedimented red cells and whole blood should be ready at the time of her infant's birth.

Compatibility. The first consideration in the selection of donor blood is immunocompatibility to insure that the red cells in the donor blood are compatible with all the maternal antibodies which may have crossed the placenta into the fetus.[1] The cross-match must always be done against maternal serum,* which is more accurate for this purpose than infant's blood. For a repeat transfusion the red cells in the second unit of donor blood must be compatible with the antibodies in the plasma of the first unit, which may still be in the infant's circulation.

Still unsettled is the importance of antibodies in the plasma of the donor blood, which may react with the cells in the fetal circulation (a "minor" mismatch) to cause hemolysis and further bilirubinemia. Generally, group O Rh-negative blood is used in exchange transfusions for Rh or ABO incompatibility. Because group O blood contains a variable amount of anti-A and anti-B antibodies, it is customary to use blood from donors who have a low titer of these antibodies, in case the infant is group A or B instead of O ("low titer O-negative blood"). Most hospitals keep a fresh unit of such blood on hand. If the infant is group A or B and the mother is of the *same* group, then the problem is resolved by using donor blood which is Rh-negative and of the same blood group. However, if mother and infant are not of the same group in the ABO system, then group O blood is used.

Formerly, the anti-A and anti-B in the donor blood was neutralized by adding Witebsky substance, a porcine A and B antigen. This neutralized anti-A and anti-B of the IgM type but was less effective in neutralizing IgG anti-A and anti-B which could also be present in low titer O, Rh-negative blood. The possible consequences of putting pork antigen into a human are still unknown and the method is seldom used.

Group O Rh-negative cells may be packed, the plasma with most of the anti-A and anti-B antibodies removed, and the cells resuspended in Group AB, Rh-positive plasma. This produces a mixture in which cells as well as plasma are compatible with everything in the infant's circulation under the usual circumstances and is theoretically superior to low titer O Rh-negative blood. It is not yet clear whether it is of practical advantage for diminishing subsequent anemia or hyperbilirubinemia.[7]

*In Rh or most other blood group isoimmunization, each successively affected infant is usually more severely diseased, except in ABO isoimmunization, where the reverse is generally true and past maternal history is less useful.

*Infants transferred to another hospital for exchange transfusion should always have a fresh specimen of maternal serum sent with them.

Temperature. The donor blood should be warmed toward neutral (37°C; 98.6°F) before infusion into a newborn infant. The replacement, twice over, of the infant's blood volume with refrigerated donor blood can produce significant hypothermia, and it considerably increases his oxygen requirements during the body's attempt to return to normal temperature. Furthermore, if the catheter tip is near the right atrium, a jet of cold blood could strike the wall of the right atrium and the conduction system of the heart and cause cardiac arrhythmia. Blood can be easily warmed by connecting the tubing from the donor bottle to a coil of plastic tubing (available commercially) and put in a 37°C water bath. Exposure to temperatures greater than 37°C can cause erythrocyte injury and lead to hemolysis.

Hematocrit. Donor blood has a subnormal hematocrit because of dilution by the acid-citrate-dextrose (ACD) anticoagulant. If the bottle or bag is not shaken repeatedly, the blood will settle during the exchange and if the whole unit is used the baby will then receive blood of very low hematocrit toward the end of the exchange and be left anemic. When blood has settled enough so that there is a distinct level separating supernatant plasma from the red cell mass, even the top 1 or 2 cm of cell mass will have a very low hematocrit and reduce that of the baby. The donor blood hematocrit is important not only because of its immediate effects but because the late anemia, which can occur several weeks after exchange transfusion, is most severe in infants who have low hematocrit at the end of the last exchange tranfusion. Caution must be used in manipulation of hematocrit because, in an attempt to avoid or correct anemia, the baby can be made polycythemic, with resultant circulatory embarrassment. The most physiologic hematocrit for extrauterine life is 43 to 45 per cent.

After the blood settles, 50 to 100 ml of plasma can be removed and the remainder used with continuous shaking. It is best to order the blood in a plastic bag with multiple satellite transfer packs, so that the plasma can be removed into one of the satellite packs without entering the unit and risking contamination. Allen and Diamond allow the blood to settle in a bottle that is laid on its side, then withdraw it from the zone midway between top and bottom during the first half of the exchange, after which they turn the bottle gently upright and use the settled cells from the lower side of the bottle.

Chemical composition is another important factor in donor blood. There is more than enough ACD in donor blood to bind all the calcium in the unit; the excess will bind such divalent cations as calcium and magnesium in the baby's circulation. The combined effect of this binding and flushing out by the exchange process lowers the concentration of ionized calcium and magnesium. The degree to which this occurs depends on the rate at which the exchange transfusion is conducted, as well as on the total volume. When the process is slow enough, calcium reserves are mobilized and the serum concentration is maintained at a safe level. Since symptomatic hypocalcemia can occur, a slow periodic infusion of calcium throughout the exchange transfusion is customary.[1] Hypomagnesemia may be a very important factor because of the potent effects of this ion upon the vascular smooth muscle.

Even recently collected ACD-anticoagulated donor blood has a very low pH. The exact chemical composition varies from unit to unit, but three- or four-day-old ACD blood has a mixed metabolic and respiratory acidosis, a pH of 6.7 or less, pCO_2 of 80 or 90 mm or more, and a base deficit of at least 15 mEq per liter. The metabolic component of the acidosis is due to the combined effects of anaerobic metabolism with an accumulation of lactate and the acid citrate of the anticoagulant. When transfused into the circulation of a vigorous full-term newborn infant, the blood is buffered, the excess CO_2 removed by the lungs, and the citrate metabolized. If these compensatory mechanisms are adequate, there is a transient acidosis and, as the citrate is metabolized, the compensated infant may become alkalotic. On the other hand, a premature infant, or one with compromised pulmonary function and metabolic acidosis secondary to hypoxia, will not be able to compensate adequately.[8,16] Since 90 per cent of his circulating blood is being replaced with very acidotic blood, this infant may become more acidotic and deteriorate after exchange transfusions with such blood. If the donor blood is buffered with 30 to 40 ml of 0.3 Molar tris-(hydroxymethyl)-aminomethane (THAM) added to 1 unit of ACD-blood, the pH will be brought to a reasonable range. However, two major precautions must be observed:

1. The blood should not be over-corrected; part

of the THAM is added, the blood mixed, the pH checked and more THAM added as necessary;

2. The buffering should be limited to blood used in those conditions which suggest the infant would not buffer the blood himself, as judged by the general condition, pH, pO_2 and pCO_2 of arterial blood. THAM is superior to sodium bicarbonate for this purpose because it contains much less sodium.

Freshly banked blood is generally used to avoid the higher levels of potassium found in older banked blood. Symptomatic hyperkalemia can occur when donor blood with a very high concentration of potassium is used. The moderate load of potassium in relatively fresh blood (less than a week old) is easily handled by most newborns.

There may be other characteristics of donor blood which have physiological significance, such as the amount of kinins and kininases in banked blood, which could also profoundly affect the infant's circulation.

Heparinized blood, with a higher hematocrit and a higher pH (usually more than 7.1) than ACD blood, does not affect blood calcium or magnesium levels and, because it "heparinizes" the baby, there is less clot formation at the end of the catheter. These advantages are partly offset by the difficulties in obtaining heparinized blood in some localities. It must be ordered ahead of time and used within 48 hours of its collection. When the baby becomes heparinized by an exchange with this type of blood, a counteracting dose of protamine sulfate at the end of the exchange will correct the iatrogenic clotting defect. Since part of the heparin is metabolized during the procedure, enough protamine sulfate can be given to counteract half of the amount of heparin given with the donor blood. At the end of a standard two-volume exchange, about 90 per cent of the infant's blood volume will be composed of donor blood so that the amount of heparin in the baby can be calculated on this basis. Some clinicians prefer not to give protamine sulfate because of its own toxic properties; but the heparin is soon metabolized and usually does not produce significant coagulation problems.

Albumin

Because of the bilirubin-binding properties of albumin, intravenous infusions of salt-poor albumin have been used to increase the removal of bilirubin during exchange transfusions and to prevent bilirubin toxicity in jaundiced infants who might be too ill to tolerate an exchange transfusion.[15] Two grams of salt-poor albumin per kilogram of body weight, given intravenously during the hour preceding a standard exchange transfusion, increases the amount of bilirubin removed up to 50 per cent. The albumin draws the indirect bilirubin and water into the vascular compartment, which increases the efficiency of the exchange. However, one must be certain that the infant can tolerate this expansion of blood volume. It is not yet clear whether this procedure reduces the total number of exchange transfusions required. It may be more useful in infants with low plasma albumin concentration in relation to bilirubin than in those who have more than enough albumin to bind all the available indirect bilirubin.

In newborn infants who have dangerous levels of bilirubin and are too ill to tolerate exchange, or when there is a delay in obtaining donor blood, some clinicians give albumin to prevent bilirubin toxicity. The residual bilirubin binding capacity of the plasma may be used to guide such therapy.[21] Since this technique is not generally available, one might use the serum albumin concentration as a rough guide for giving or repeating the albumin therapy. (It is not uncommon to infuse a dose of 0.5 gm per kg of body weight daily in order to maintain the albumin concentration at the desired level.)*

One objection to infusions of albumin in trying to avoid an exchange has been that, if a great deal of bilirubin is drawn out into the plasma, the bilirubin concentration will rise and can no longer be used as an indication for subsequent exchange transfusion. In our experience, the bilirubin usually rises only 1 or 2 mg per 100 ml while the hematocrit falls 1 or 2 per cent (due to hemodilution). A greater rise in bilirubin concentration would indicate much unbound bilirubin in the tissues and a more severe condition than the pre-treatment bilirubin concentration indicated. It is stronger evidence for an exchange if the bilirubin remains at this higher concentration during the next two to four hours.

Timing of the Exchange Transfusion

There are two conflicting needs in the timing of an exchange transfusion: Removal of antibody-coated red cells before they are hemolyzed, and sufficient time for the newborn infant to complete the appropriate adaptations to extrauterine life

*The concentration should be at least half again as much as is required to bind the amount of bilirubin present at pH 7.4, or even more when the infant is acidotic.

(such as adequate lung expansion, correction of immediate postnatal acidosis, beginning closure of the ductus arteriosus).

When lysis of antibody-coated red cells in the circulation occurs, their hemoglobin is converted to bilirubin in a few hours—each gram of hemoglobin in converted into about 33 mg of bilirubin. Hemoglobin within the intact red cells is distributed only within the vascular compartment and is removed easily by an exchange, whereas bilirubin is distributed more widely throughout the body and not so easily removed by exchange transfusion. It seems wise to transfuse at the earliest possible moment any infant who is predicted to need an exchange sooner or later, and thereby reduce the number of subsequent procedures.

On the other hand, provided such infants are not hydropic or severely anemic, there is no clear-cut evidence that a delay until the infant is a few hours of age will increase the need for subsequent exchange. A possible explanation for this is that, while 90 per cent of the red cells in the circulation are removed by a two-volume exchange, excess maternal anti-erythrocyte antibodies are distributed more widely throughout the body and a large fraction will remain in the infant after the exchange and coat new red cells released into the circulation from the infant's bone marrow. Thus, the added hemolysis during a two to four hour delay is an insignificant proportion of the continuing hemolysis.

Assessment of the Infant

As was stated previously, the management of each infant should be highly individualized on the basis of a thorough evaluation of physiological factors, not only the infant's hemoglobin and bilirubin concentration. The measurement of serum albumin, blood glucose and arterial or arterialized capillary blood pH, pO_2 and pCO_2 will be a better guide to management. When there are metabolic factors which enhance bilirubin toxicity, corrective therapy (such as alkali therapy for metabolic acidosis) should be begun promptly.

The infant's general condition should also be considered in choosing the environment in which the procedure is done. Sterile technique is very important, but it is not necessary to use a cold surgical amphitheater with a staff not familiar either with the procedure or with the care of newborn infants to achieve asepsis. A sick infant is much safer in an incubator or, better still, under a radiant warming unit with an oxygen mask or hood as needed and with experienced nurses in attendance.

Mechanics of the Exchange Transfusion

Catheter placement and measurement of venous pressure. The standard exchange transfusion is made through a saline-filled polyethylene catheter inserted into the umbilical vein, as described by Allen and Diamond.[1] It is important to know the position of the tip of this catheter: From the umbilical vein it enters the portal sinus within the liver. An attempt to advance it may cause it to go through the ductus venosus into the inferior vena cava about 75 per cent of the time. It occasionally turns caudally in the vena cava, but generally cephalad. If advanced far enough (about 10 to 12 cm in a full-term newborn) it will reach the right atrium. Alternately, it may not go through the ductus venosus but coil itself within the portal sinus, go off into one of the hepatic radicals or back into the portal vein.

The location is important for measuring venous pressure, assessing cardiac failure and withdrawing and injecting blood. If the catheter does *not* go through the ductus venosus, the portal venous pressure (normal about 9.9 cm of water) and not the central venous pressure will be measured. Portal is higher than central venous pressure by a variable amount, and it may be elevated due to a local phenomenon without concomitant elevation of central venous pressure.

Once through the ductus venosus and into the inferior vena cava, an accurate measurement of venous pressure can be made (normal 1.4 cm of water [SD$\pm$2.0 cm]). As the catheter is advanced, the location can be determined by the variations in pressure with respirations. In the portal sinus, the swings with respiration are small (generally only 2.4 cm of water), the pressure rising on inspiration and falling on expiration. As it goes through the ductus and into the inferior vena cava the changes are greater (5 to 13 cm of water) but still rising on inspiration.[4] When the catheter tip is above the diaphragm and in the thorax, the pressure falls with the start of each inspiration. It is not necessary to leave the catheter tip above the diaphragm—it can be pulled back just below it, with the assurance that it is in the inferior vena cava and that pressure measurements can be trusted. Since an abnormal central venous pressure has serious therapeutic implications, er-

rors in measurement must be avoided by appropriate attention to these details.

The proper position for the catheter tip during an exchange is not known. Most workers agree that it should not be in the right atrium, where a jet of donor blood unmixed with the infant's venous blood may hit the heart wall. Injecting and withdrawing blood from the portal sinus has the disadvantage of distending and contracting a structure of limited capacity. The inferior vena cava has a large volume of blood flow, particularly above the level at which the hepatic vein joins it. The usual amount of blood removed or injected here is only a small portion of the total flow, the hemodynamic effect is less and there is some mixing by the time the blood reaches the heart.

The exchange transfusion itself is a simple flushing out of the intravascular space. The blood does not flow steadily in and out of the baby but is removed and replaced in increments of 10 to 20 ml. The first syringefull (increment) removed is only the baby's blood but, as the procedure goes on, more of the blood removed with each cycle is donor blood infused during the earlier cycles. From this has come the erroneous belief that the use of larger increments would give a more efficient exchange for any given total volume exchanged. Dangerously large volumes of blood are thus sometimes removed in each increment in the mistaken belief that more bilirubin is being washed out. This is true theoretically but of no practical consequence.[18] As an illustration, consider a one-volume exchange transfusion in a newborn infant with a blood volume of 300 ml. If the entire blood volume could be removed in one increment and then replaced with donor blood, the *vascular compartment* (but not the extracellular fluid space) would have been flushed out with an efficiency of 100 per cent. If half the blood volume (150 ml) is removed at once (still an unthinkably large amount) and replaced, then 150 ml removed again and replaced, the efficiency would be only 75 per cent. As the ratio of the increment volume to the infant's blood volume gets smaller, the efficiency decreases toward a minimum value of 63 per cent—the same efficiency as one would get with steady flow through the baby. Within the range of practicality, there is nothing to be gained by using a larger volume: For example, the efficiency of an exchange transfusion using 30 ml increments is insignificantly greater than one using 5 ml increments.

The potential disadvantage of larger increments is the stress put upon the infant's cardiovascular adaptive mechanisms by repeatedly removing and reinfusing one-fifteenth to one-tenth of his total blood volume.[23]

The lower limit of the increment to be used is set by the dead space of the catheter and stopcock which connects the syringe to the infant's circulation. The blood in this dead space is not really exchanged. At the end of the "in" phase of each cycle, donor blood is left in the dead space; with the next "out" phase, this unmixed donor blood comes into the syringe before any of the baby's blood is removed. Not until the dead space equals one-tenth the volume removed in the syringe does this significantly affect the efficiency of the process. This problem can be managed either by using a narrower catheter with a smaller volume or by flushing the catheter at the end of each "in" phase by drawing back twice the volume of the dead space and reinfusing it.

Since the usual exchange with 10 to 20 ml increments is no more efficient than a steady flow of blood into and out of the infant, this latter method has been used without producing any change in the blood volume. Valentine[19] has heparinized the infant and withdrawn the blood from the umbilical vein at the same rate as it was infused into the saphenous. This can also be done through a double lumen catheter via the umbilical vein. An indwelling catheter is often placed in the umbilical artery of a sick infant for serial determinations of blood gases. If such an infant needs an exchange transfusion, a second catheter in the umbilical vein will permit a continuous exchange into the venous catheter and out the arterial.

The efficiency with the usual exchange transfusion technique is shown in the following tabulation:

Volume of Blood Used (Per Cent of Baby's Blood Volume)	*Per Cent of Baby's Original Blood Replaced by Donor Blood*
0.5	40
1.0	65
2.0	85
3.0	95

The original hematocrit and that of donor blood can help to predict the baby's hematocrit at the end of an exchange procedure of a given volume. Only a small exchange with sedimented or packed red cells is needed to correct a low hematocrit

rapidly. Continuing the exchange beyond twice the infant's blood volume will do little to remove antibody-coated red cells.

These figures on the efficiency of the exchange are for the washout of the vascular compartment only, and do not apply to the removal of bilirubin.[3,18] At the end of the standard two-volume exchange the concentration of bilirubin will still be approximately half that at the start, yet the bilirubin removed and in the exhaust bucket will be twice the amount circulating in the plasma at the start (Chart 2). Obviously, a great deal of bilirubin must have entered the circulation during the course of the exchange.

Bilirubin equilibration. Indirect bilirubin behaves as though it is distributed into three spaces[18]: The circulating plasma and two extravascular compartments—one of which equilibrates very rapidly with the circulating plasma (presumably extravascular-extracellular fluid) and the other (intracellular?) which equilibrates very slowly with the other two spaces. The first two are in such close communication that they are, in effect, one. As soon as the concentration in the plasma falls even slightly, bilirubin moves from the extracellular fluid into the plasma until equilibrium is reached. As to bilirubin removal, the exchange transfusion flushes out a much larger space than just the vascular compartment.[3,18] In order to move bilirubin from the slowly equilibrating pool into the extracellular fluid and plasma, a high concentration gradient and a long time is required. Such a gradient is not established until later in the exchange transfusion when a large amount of bilirubin has been washed out of the plasma and other extracellular fluid. Since the albumin in the donor blood is not saturated with bilirubin, it, too, contributes to the movement of bilirubin into the vascular space.

This slower equilibration process contributes to the post-exchange rise (rebound) in bilirubin concentration in the four hours after the procedure has ended. So little of this bilirubin moves into the plasma during a standard exchange transfusion that there is no great advantage in a slower one in the hope of removing more bilirubin as this equilibration occurs, unless one is willing to prolong the procedure at least another one or two hours. Valentine[19] uses his continuous exchange technique to do very slow exchanges (four hours or more) to permit this equilibration to occur and more bilirubin to be removed.

The amount of bilirubin removed at any point in the course of an exchange transfusion depends upon the concentration of bilirubin in the plasma at that point. As the bilirubin concentration falls, so does the amount removed; therefore, two separate two-volume exchanges can remove more bilirubin than one four-volume exchange. Generally, after one two-volume exchange, the plasma bilirubin concentration is low enough that it is wiser to wait four hours before considering another exchange. Occasionally, however, the initial bilirubin is so high or the hemolytic process so severe that additional bilirubin is produced during the time of the exchange, and the concentration is still high at the end of a standard exchange transfusion. A great deal more bilirubin, therefore, can be removed by extending the procedure to an exchange of three or even four times the baby's blood volume. Although even more bilirubin would

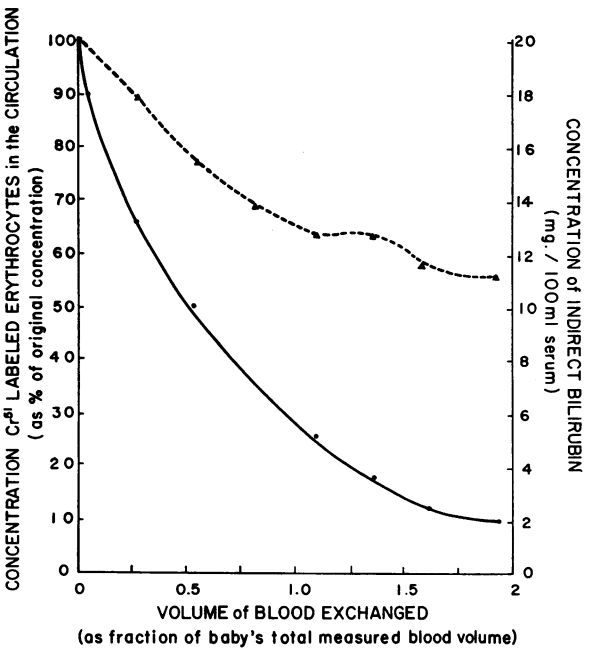

Chart 2.—The efficiency of an exchange transfusion in a 2,865 gm newborn. Cr^{51}-labeled red cells had previously been infused into the infant's circulation; the fall in their concentration (solid line) during the exchange transfusion is a measure of the efficiency with which the vascular compartment is washed out. Note that the fall in indirect bilirubin concentration (dotted line) is not as great. The difference between the two lines is due to the indirect bilirubin which has moved from extravascular areas into the vascular compartment during the procedure. The baby had a total of 33.2 mg of indirect bilirubin in his intravascular compartment at the start of the exchange. A total of 43.9 mg of indirect bilirubin was removed by the procedure, yet the serum concentration was only halved, and 18.9 mg remained in his vascular space at the end, so that 29.6 mg moved into the vascular space during the exchange. (Graph derived from the data of Sproul and Smith.[18])

be removed by waiting four hours before the next exchange, the bilirubin would climb to very dangerous levels. Chart 3 illustrates such an exceptional case, which indicates that occasionally there is a place for larger exchanges.

Post-Exchange Tranfusion Management

The principles of management of any exchange after the first one are implicit in the preceding discussion. Hematocrit or hemoglobin must be remeasured, all the critical variables should be reevaluated serially, and the first bilirubin measured three to four hours after the exchange when the rebound due to re-equilibration is over. This measurement should not be postponed, no matter how certain that another exchange will not be needed. Platelets should also be evaluated by peripheral smear, and by count if they appear low. A moderate transient thrombocytopenia commonly occurs after an exchange transfusion; however, in infants with severe hemolytic disease, thrombocytopenia may be severe and prolonged and require treatment with very fresh blood or platelet transfusions. Depletion of other clotting factors by exchange transfusion has yet to be evaluated.

The incidence of positive blood cultures at the end of exchange has been high enough that many clinicians give antibiotics afterward. The need for such therapy undoubtedly varies inversely with the quality of sterile technique during the procedure.

There are definite hazards and no particular advantages in leaving the catheter in the umbilical vein for a prolonged period after the exchange. Usually, the vein can be reentered easily if another exchange is needed. If necessary, one can cut down on the umbilical vein, which runs longitudinally just under the skin, by a transverse incision about 1 cm cephalad of the umbilical stump.

Finally, when an infant with hemolytic disease is discharged from the nursery, one must not forget the late anemia (see section: Donor Blood) which is most severe at one to two months of age and may require a simple transfusion.

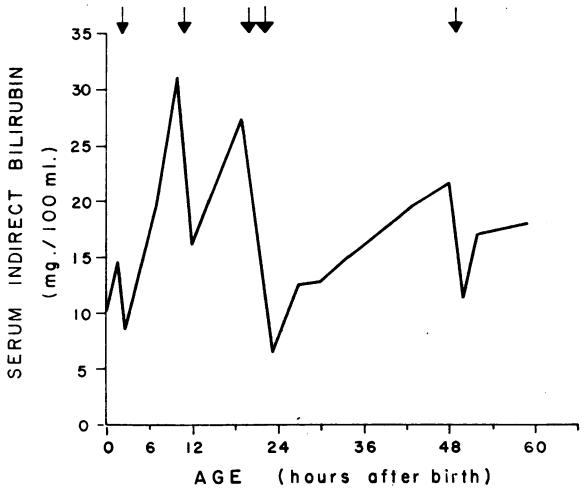

Chart 3.—↓=Standard "two-volume" exchange transfusion. ↓↓="four-volume" exchange transfusion.

Course of severe Rh hemolytic disease in a full-term newborn. The rapidly rising bilirubin after the first exchange was a clue that a four-volume exchange might be needed. The second two-volume exchange halved the bilirubin concentration but, since it was 17 mg per 100 ml at the end, continuing the exchange would have removed much more bilirubin. The four-volume exchange reduced bilirubin to one-fourth the pre-exchange level, and the post-exchange rise was much slower.

Note delay in repeat exchanges due to failure to anticipate the need for several units of donor blood.

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